REMARKS/ARGUMENTS

I. STATUS OF THE CLAIMS

With entry of this amendment, claims 63, 64, 66, and 68-74 are pending. Claim 67 is canceled and claims 63, 64, 66 and 71 are amended. No new matter is added. For convenience, reference to the instant application shall refer to the Pre-Grant Publication No. 2004/0038317.

II. CLAIM AMENDMENTS

Support for the claims as presently amended can be found throughout the specification and at least in the priority document 09/526,106, filed March 15, 2000. Claim 63 is presently amended to clarify that the fragment complementation system is comprised of a first oligopeptide sequence and a second oligopeptide sequence. Support for this amendment can be found throughout the specification, for example, in paragraph [0028] of the Pre-Grant Pub., and page 9 lines 29-30 of the '106 application which states "[t]he fragment pairs are used in methods that involve the co-expression of a first and a second oligopeptide sequence...." Claim 63 is also amended to clarify that the first and the second oligopeptide sequences are fusion proteins. Support for the composition of the first oligopeptides sequence fusion protein and the second oligopeptides sequence fusion protein can be found in paragraph [0028] of the Pre-Grant Pub. and at page 9, line 30 to page 10, line 3 of the '106 application, which states that:

> ...the first oligopeptides sequence is a fusion protein comprised of in the direction of translation, an N-terminal fragment fused through a break-point terminus to a flexible polypeptide linker and a first interactor domain, and the second oligopeptides sequence is a fusion protein comprised of in the direction of translation, a second interactor domain and a flexible polypeptide linker fused through a break-point terminus to a C-terminal fragment.

Furthermore, in response to the Examiner's concern that the Applicants are not in possession of fragments less than 25 amino acids in length, the Applicants have incorporated a limitation into claim 63 that the fragments are at least 25 amino acids in length. Support for this limitation can be found throughout the specification, for example in paragraph [0042] of the Pre-

Grant Pub. and at page 16, lines 4-5, of the '106 application which states that "fragments of less than 25 amino acids were considered non-viable."

Claim 64 is currently amended to correct antecedent basis for "a" host cell. Claim 66 is amended to include the sequence from figure 2, which is identical to that shown in SEQ ID NO:2, with the exception that the numbering of the amino acids in figure 2 takes into account that the first 25 amino acids (not shown in the figure) represent a signal peptide sequence. Support for the sequence in claim 66 can be found throughout the specification, for example, in Figure 2 of both the Pre-Grant Pub. and the '106 application. Claim 66 is also amended to recite particular junctions for locating break-point termini, which correspond to the numbering of the sequence as shown in claim 66 and in figure 2. Support for the break-point termini can be found throughout the specification, for example in paragraph [0042] of the Pre-Grant Pub. and page 16, lines 22-25 of the '106 application. Claim 71 is amended to delete that information that is currently incorporated into claim 63, specifically, that the first and second oligopeptides sequences each comprise a linker that separates the Class A β-lactamase protein fragment from the interactor domain.

No new matter is added with entry of this amendment and the claims are currently amended are supported both by the instant application (Pre-Grant Pub.) and the '106 application, filed March 15, 2000, of which the instant application is a continuation.

III. PRIORITY

The present application is a continuation of U.S. App. No. 09/526,106 ('106 app.) filed on March 15, 2000, which claims benefit of U.S. Prov. App. No. 60/175,968 ('968 app.) filed on January 13, 2000, and claims benefit of U.S. Prov. App. No. 60/135,926 ('926 app.) filed May 25, 1999, and claims benefit of U.S. Prov. App. No. 60/124,339 ('339 app.) filed March 15, 1999. The Examiner alleges that one or more of the applications stated above fail to provide adequate support under 35 U.S.C. §112 first paragraph for specific aspects of the claimed invention as detailed on page 3 of the Office Action. The Examiner therefore alleges that the filing date for the instant application is the actual filing date of September 22, 2003. Furthermore, the Examiner alleges that because the instant application contains data that is not

described in any of the priority applications, the Applicant is required to change the relationship to the prior-filed application from a continuation or divisional application, to a continuation in part application. For at least the reasons discussed in more detail below, and in section V addressing the New Matter rejections, Applicants disagree.

Adequate support under 35 U.S.C. §112 first paragraph for the invention as presently claimed can be found in the instant application as filed and in the priority documents, particularly the '106 app. filed on March 15, 2000, of which the instant application is a continuation.

With regard to the genus of fragment complementation systems comprising a first Class A β-lactamase protein break-point as presently recited in independent claim 63, Applicants direct the Examiner's attention to the support identified in Section II discussed above, and to Section V regarding the New Matter rejections discussed below.

With regard to support for specific peptide segments that enhance functional reconstitution, as recited in claims 68-70 and 72-74, Applicants direct the Examiner's attention to Example 6, in particular, paragraph [0097] of the Pre-Grant Pub, and page 46, lines 5-12 of the '106 application, filed March 15, 2000. Moreover, this same table listing the specific tri-peptides HSE, EKR, QGN, DGR, GRR and GNS can also be found on page 17, of priority App. No. 60/175,968, filed January 13, 2000.

In view of the identified support for the claimed invention as discussed above, Applicants request that the Examiner acknowledge the status of the present application as a continuation of 09/526,106 filed March 15, 2000 which claims benefit of U.S. Prov. App. No. 60/175,968 ('968 app.) filed on January 13, 2000, and claims benefit of U.S. Prov. App. No. 60/135,926 ('926 app.) filed May 25, 1999, and claims benefit of U.S. Prov. App. No. 60/124,339 ('339 app.) filed March 15, 1999.

IV. REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 63, 66, 67 and 71-74 stand rejected under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner alleges that the phrase "wherein said first class

A β-lactamase protein break-point and said second Class A β-lactamase protein break-point..." lack sufficient antecedent basis. Specifically, the Examiner alleges that the claim previously refers to a first and second "oligopeptides," not a first and second "break-point."

Applicants disagree.

Claim 63 as pending prior to entry of this amendment had sufficient antecedent basis. Specifically, line 4 of the claim prior to entry of this amendment stated "...through the C-terminus of a first Class A β-lactamase protein break-point..." (emphasis added). Similar language providing antecedent support for the second break-point can be found in line 7 of claim 63 prior to entry of this amendment. Furthermore, Applicants contend that claim 63 as presently recited provides adequate antecedent basis for "...**a first break-point** terminus...and...**a second break-point** terminus..." (emphasis added).

In view of the above, Applicants request that the Examiner withdraw the rejection.

V. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH - NEW MATTER

Claims 63, 66, 67 and 71-74 stand rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor was in possession of the claimed invention at the time the application was filed. Specifically, the Examiner alleges that the application does not provide support for "wherein said first Class A β-lactamase protein break-point and a second Class A β-lactamase protein break-point are within 10 amino acids in either direction from a junction between 2 amino acids residues, wherein said 2 amino acid residues are within a solvent exposed loop between elements of secondary structure...." Furthermore, the Examiner alleges that the Applicants are not in possession of fragments less than 25 amino acids, and that there is no support for the junctions as set forth in claim 67. In view of the claims as presently recited and for the reasons presented *supra*, and discussed in more detail below, Applicants respectfully disagree.

With regard to claim 63, the Examiner alleges that the previously identified support on page 16 does not refer to the passage on page 13, but rather only to the passage

immediately preceding it, which describes the E197/L198 break-point. Applicants disagree. The E197/L198 break-point is only a single example of possible break-points that can be used with the invention, and merely illustrates the success of the method of searching the fragment space of a marker protein to identify suitable fragment pairs. The method of searching the fragment space includes introducing break-points into solvent exposed or flexible loops as described in paragraph [0037] of the Pre-Grant Pub. and at page 13, lines 16-19, of the '106 application. The break-point E197/L198 merely illustrates a fragment pair identified using the method wherein the break-point is located in a solvent exposed loop and the fragment pair can be reconstituted using fos and jun as interactor domains, as disclosed in paragraph [0042] of the Pre-Grant Pub. and page 16 of the '106 application. Therefore, contrary to the Examiner's assertion, the passage cited in paragraph [0042] of the Pre-Grant Pub. and page 16, lines 26 to 28 of the '016 application, do refer to the general method as disclosed in paragraph [0037] of the Pre-grant Pub and page 13 lines 16-19 of the '106 application.

In addition to the support identified above, further support for locating the break-point within a solvent exposed loop can be found in Example 5 (particularly paragraphs [89-90] and Table 5 of the Pre-Grant Pub.) and the passage from the bottom of page 40 to the top of page 41 along with Table 5 in the '106 application. In particular, the referenced passages state:

> "This idea was tested by screening nine additional pairs of TEM-1 b-lactamase fragments, corresponding to scission in nine exposed loops of the polypeptide chain. The non fragment pairs were screened for selectable activity with the break-point disulfide alone, the fos-jun interaction alone, and with both together. The results are summarized in Table V." (Emphasis added).

Among the specific fragment pairs listed in Table V are each of the specific break-points presently recited in claim 66. Thus, the Applicants were in possession of the claimed subject matter at the time the application was filed.

In view of the arguments presented above, and the claims as presently presented, Applicants request that the Examiner withdraw the rejection.

With regard to the Examiner's allegation that the Applicants were not in possession of fragments less than 25 amino acids in length, Applicants note that each of the

fragments as specifically claimed is greater than 25 amino acids in length. Specifically, as can be seen from Figure 2, the β-lactamase sequence is 263 amino acids in length (numbered from 26-288). The shortest N-terminal fragment results from a break-point at N52/S53, with the N-terminal fragment being 27 amino acids in length. Similarly, the shortest C-terminal fragment results from a break-point G 253/K254, with the C-terminal fragment being 34 amino acids in length. Therefore, none of the disclosed break-points result in fragments less than 25 amino acids in length. In an effort to expedite prosecution of the application, however, Applicants have amended claim 63 to introduce a limitation that the Class A β-lactamase fragments are at least 25 amino acids in length.

With regard to the junctions set forth in claim 67, which are hereby incorporated into claim 66 as currently amended, have been renumbered to be consistent with the text of the specification and with the enumeration as shown in Figure 2. Support for the break-points can be found throughout the specification, in particular, in Figure 2 paragraph [0042] of the Pre-Grant Pub. as indicated *supra*. The break-points as previously numbered, prior to entry of this amendment, were enumerated as shown in SEQ ID NO:2. Although this sequence is identical to that shown in Figure 2, the numbering is different. The numbering of the amino acid residues as shown in Figure 2 begins with the histidine as residue 26. This numbering reflects the fact that the first 25 amino acids are a signal peptide that are not included in the sequence as shown. The sequence as shown in SEQ ID NO:2 (which is identical to that shown in Figure 2) begins numbering at position 1, as required by the MPEP §2423.03 and 37 C.F.R. §1.822(d). Claim 66 has been amended to include the sequence (and numbering) as shown in Figure 2, which is also the numbering as referred to throughout the text of the specification.

In light of the above, and the claims as presently recited, Applicants request that the Examiner withdraw the rejection.

VI. REJECTIONS UNDER 35 U.S.C. §102

Claims 63, 66, 67, 71 and 72 stand rejected under 35 U.S.C. §102(b) as anticipated by Wehrman *et al.* PNAS March 19, 2002, 99(6):3469-3474. The Examiner alleges that Wehrman *et al.* discloses a β-lactamase complementation system which anticipates the

claimed invention. Specifically, with regard to independent claim 63, the Examiner alleges that Wehrman *et al.* discloses, *inter alia,* a fragment complementation system comprising a first oligopeptide comprising an N-terminal fragment of a Class A β-lactamase protein covalently bonded through the C-terminal break-point to a first interactor domain. Wehrman *et al.* is also cited as disclosing a second oligopeptide comprising a C-terminal fragment of a Class A β-lactamase protein covalently bonded through the N-terminal break-point to a second interactor domain. With regard to claim 66, Wehrman *et al.* is cited as disclosing a fragment complementation system where the Class A β-lactamase protein comprises SEQ ID NO:2. With regard to claim 67, the Examiner alleges that Wehrman *et al.* discloses a fragment complementation system where the first break-point and the second break-point are within 10 amino acids in either direction from a junction between 2 amino acid residues in SEQ ID NO:2. With regard to claim 71, the Examiner cites Wehrman *et al.* as disclosing polypeptide linkers 3-30 amino acids in length. With regard to claim 72, Wehrman *et al.* is relied upon as teaching tri-peptides HSE, GRE, EKR, and NGR. To the extent that the rejections apply to the claims as presently amended, Applicants disagree.

As discussed above, the present application is a continuation of 09/526,106, filed 3/15/00, which claims benefit of which claims benefit of U.S. Prov. App. No. 60/175,968 ('968 app.) filed on January 13, 2000, and claims benefit of U.S. Prov. App. No. 60/135,926 ('926 app.) filed May 25, 1999, and claims benefit of U.S. Prov. App. No. 60/124,339 ('339 app.) filed March 15, 1999. As indicated *supra*, each of the claim elements allegedly disclosed in Wehrman *et al.* is disclosed at least in the parent application (09/526,106) filed on March 15, 2000, which is nearly 2 years prior to the March 19, 2002 publication date of Wehrman *et al.* Therefore, Wehrman *et al.* is not prior art to the presently claimed invention. Because Wehrman *et al.* is not prior art to the presently claimed invention, Wehrman *et al.* cannot anticipate the claimed invention.

In light of the above, the Applicants request that the Examiner withdraw the rejection.

VII. REJECTIONS UNDER 35 U.S.C. §102/103

Claims 63, 66, 67 and 71 stand rejected under 35 U.S.C. §102(e) as anticipated, or in the alternative, under 35 U.S.C. §103(a) as being unpatentable over Michnick *et al.* (U.S. Pat. No. 6,828,099) filed May 31, 2001, alone or in view of Galarneau *et al. Nat. Biotech.* 2002, 20:619-622, as evidenced by Applicants Exhibit 1 filed October 26, 2006.

Applicants disagree.

As discussed above, the present application is a continuation of 09/526,106, filed 3/15/00, which claims benefit of which claims benefit of U.S. Prov. App. No. 60/175,968 ('968 app.) filed on January 13, 2000, and claims benefit of U.S. Prov. App. No. 60/135,926 ('926 app.) filed May 25, 1999, and claims benefit of U.S. Prov. App. No. 60/124,339 ('339 app.) filed March 15, 1999. As discussed *supra*, the claims as presently recited claim priority at least to the '106 application filed March 15, 2000, which is 1 year prior to Michnick *et al.*, and two years prior to Galarneau *et al.* Therefore, the cited references are not prior art to the presently claimed invention. Because the cited references are not prior art, the cited references cannot anticipate the invention as presently claimed.

Furthermore, the present invention is not obvious in view of the cited references because the fusions of the interactor domains to the β-lactamase fragments in the claimed orientation as alleged to be shown in Galarneau *et al.* would not be within the knowledge of a skilled artisan as of the priority date of the present application, because Galarneau *et al.* was not publicly available as of the priority date of the present application.

Because neither Michnick *et al.* nor Galarneau *et al.* are prior art with regard to the presently claimed invention, the cited references cannot anticipate, nor render the invention as claimed unpatentable.

In light of the above, the Applicants request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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Attachments
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